Making Sense: Dopamine Activates Conscious Self-Monitoring Through Medial Prefrontal Cortex

Morten Joensson,[1,2] Kristine Rømer Thomsen,[1,2,3] Lau M. Andersen,[1,4] Joachim Gross,[5] Kim Mouridsen,[1] Kristian Sandberg,[1,4,6] Leif Østergaard,[1] and Hans C. Lou[1]*

[1]Center of Functionally Integrative Neuroscience, Aarhus University, 8000 Aarhus, Denmark
[2]Department of Psychiatry, University of Oxford, OX37JX Oxford, United Kingdom
[3]Centre for Alcohol and Drug Research, Aarhus University, 8000 Aarhus, Denmark
[4]Cognitive Neurosciences Research Unit (CNRU), Hammel Neurorehabilitation Centre and University Research Clinic, Aarhus University, Nørrebrogade 44, Building 10G, 8000 Aarhus C, Denmark
[5]Centre for Cognitive Neuroimaging, University of Glasgow, Glasgow, United Kingdom
[6]UCL Institute of Cognitive Neuroscience, University College London, Alexandra House, 17 Queen Square, London WC1N 3AR, UK

Abstract: When experiences become meaningful to the self, they are linked to synchronous activity in a paralimbic network of self-awareness and dopaminergic activity. This network includes medial prefrontal and medial parietal/posterior cingulate cortices, where transcranial magnetic stimulation may transiently impair self-awareness. Conversely, we hypothesize that dopaminergic stimulation may improve self-awareness and metacognition (i.e., the ability of the brain to consciously monitor its own cognitive processes). Here, we demonstrate improved noetic (conscious) metacognition by oral administration of 100 mg dopamine in minimal self-awareness. In a separate experiment with extended self-awareness dopamine improved the retrieval accuracy of memories of self-judgment (autonoetic, i.e., explicitly self-conscious) metacognition. Concomitantly, magnetoencephalography (MEG) showed increased amplitudes of oscillations (power) preferentially in the medial prefrontal cortex. Given that electromagnetic activity in this region is instrumental in self-awareness, this explains the specific effect of dopamine on explicit self-awareness and autonoetic metacognition. *Hum Brain Mapp 36:1866–1877, 2015*.

Key words: dopamine; self-awareness; metacognition; medial prefrontal; default mode

The copyright line for this article was changed on 17 July 2015 after original online publication.

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: MINDLab Investment Capital for University Research Fund (M.J., K.R.T., K.M., L.Ø., and H.C.L.); Contract grant sponsor: JG was supported by the Wellcome Trust [098433]; Contract grant sponsor: European Research Council (K.S.); Contract grant sponsor: Aarhus University (L.M.A.); Danish Council for Independent Research (H.C.L); Carlsberg Foundation (K.S.)

*Correspondence to: Hans C. Lou; CFIN, Aarhus University Hospital, DK-8000 Aarhus, Denmark. E-mail: hanslou1@gmail.com

Received for publication 4 December 2014; Accepted 12 January 2015.

DOI: 10.1002/hbm.22742

Published online 27 January 2015 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

During evolution, increasingly sophisticated brains allow organisms to survive longer by learning from experience and predicting future events [Ingvar, 1985]. This adaptability to internal and external events increases the demand for selective resource allocation according to needs. It raises the questions of how the brain controls its own cognitive processes, how it learns from previous personal experiences, and how prediction of future events occurs [Lou et al., 2011b]. Despite the fundamental significance for human nature of self-monitoring and the development of new strategies for treatment of its dysfunction [Bechara, 2005; McNab et al., 2009; Rømer Thomsen et al., 2013; Tang et al., 2010], its neurotransmitter regulation has remained unknown.

Conscious self-monitoring, or metacognition, is dependent on self-awareness [Frith, 2012]. Self-awareness comes in two different categories: Minimal self-awareness and extended self-awareness. Minimal self-awareness is "consciousness of one-self as an immediate subject of meaningful experience, unextended in time" [Gallagher, 2000]. Minimal self-awareness allows "noetic" (or "conscious") metacognition. When it is efficient, it implies that the subjective experience of awareness is a predictor of performance in tasks influenced by such experience. As an example, we will demonstrate in *Experiment 1* that subjective experience of rapidly presented words is a predictor of efficiency of identifying such words in a forced choice paradigm [Metcalfe and Son, 2012]. Extended self-awareness is "extended in time to include memories of the past and intentions toward the future" [Gallagher, 2000]. Its basis is retrieval of personal memories which may have different degrees of explicit self-reference or introspection [Gallagher, 2000]. A high degree of introspection is equivalent with "autonoetic" metacognition [Metcalfe and Son, 2012]. One way of quantifying autonoetic metacognition is therefore to determine retrieval efficiency of episodic memories with explicit self-reference.

In a previous positron emission experiment, the emergence of meaningful conscious experience with minimal self-awareness was directly linked to increased hemodynamic activity in a paralimbic network. This network includes medial prefrontal and medial parietal/posterior cingulate (PCC) cortices as key cortical regions, together with thalamus, and striatum [Kjaer et al., 2001]. The increased paralimbic activity occurred when the appearance of flickering stimuli was replaced by the appearance of written words by prolonging the exposure time at the expense of the number of exposures [Kjaer et al., 2001]. Later studies showed that the network is selective, active, and instrumental in explicit self-awareness [Kjaer et al., 2002b; Kwan et al., 2007; Lou et al., 2004; Luber et al., 2012; Newen and Vogeley, 2003]. The interaction between the major cortical regions depends on recurrent and synchronized electromagnetic activity in the gamma range (30–100 Hz) [Lou et al., 2011a] which is most pronounced with a high degree of self-reference [Lou et al., 2010].

Circumstantial evidence has suggested that the neurotransmitter dopamine is closely linked to conscious experience [Kjaer et al., 2002a; Schmitt et al., 2006]. More recently, we provided the first direct evidence that dopamine regulates subjective conscious experience by showing that dopamine stimulation enhances confidence and performance when seeing rapidly presented words [Lou et al., 2011c]. No previous studies have specifically examined the role of dopamine in the regulation of metacognition. With this aim, the present study investigated the effect of dopaminergic stimulation in simple perceptual awareness with noetic metacognition and in retrieval of explicitly self-related judgment (autonoetic metacognition).

Two experiments were conducted: (1) A behavioral study investigating the online effect of dopamine stimulation on perception, subjective awareness and noetic metacognitive capacity of visually presented words related to one self or another person (Fig. 1) and (2) A combined behavioral and magnetoencephalographic (MEG) study investigating the effect of dopamine stimulation on

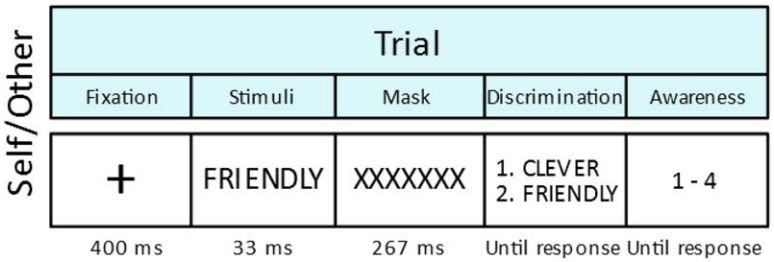

Figure 1.

Experimental design for minimal self-awareness task (visual identification). On each trial of Experiment 1, participants had to identify a briefly presented (33ms) and masked trait adjective. The participant was required to rate how aware they were of the stimuli on a perceptual awareness scale. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

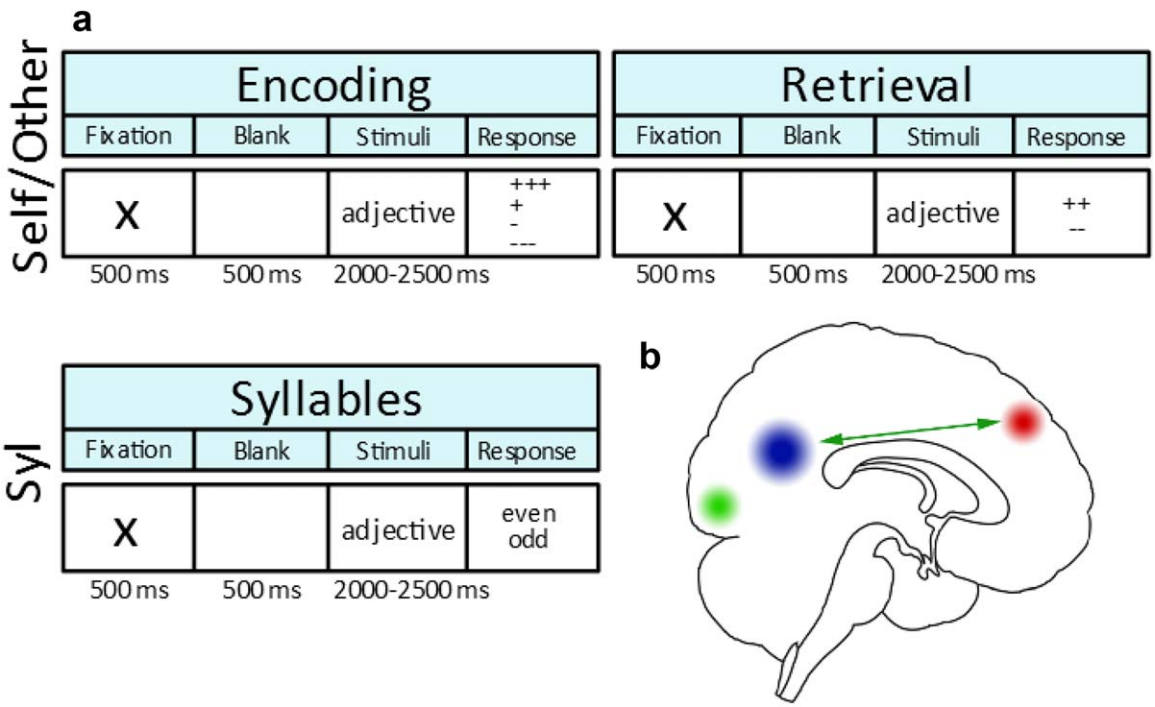

Figure 2.

Experimental paradigm for extended self-awareness task. (**a**) The participants first rated trait adjectives on how well they fitted themselves (self-task) or the Danish Queen (other-task). The encoding block was followed by a retrieval block, where the same words were presented in a randomized order and the participants responded whether the word was previously judged fitting or not. In the third task the participants rated whether the trait adjective had an even or odd number of syllables. (**b**) Talairach coordinates used for MEG source extraction were: medial prefrontal cortex (red): ($x = 0$, $y = 42$, $z = 54$); PCC (blue): ($x = 0$, $y = -50$, $z = 28$); V1 (green): ($x = 29$, $y = -96$, $z = -6$). Coordinates correspond to peak activities from a PET-study investigating the paralimbic network [Lou et al., 2004]. The figure is modified from [Rømer Thomsen et al., 2013].

episodic retrieval of words related to one self (autonoetic metacognition) or another person and on activity in the paralimbic network (Fig. 2a).

In Experiment 1, the influence of dopaminergic stimulation was examined by giving half of the participants Sinemet (100 mg of the dopamine precursor L-DOPA and 25 mg carbidopa), and the other half placebo in a double blind experiment. Participants rated how well trait adjectives described either themselves or a person known to all participants (the Danish Queen) on a four-point scale. Several days later they performed a visual identification task (Fig. 1) and reported awareness of perception using the Perceptual Awareness Scale (PAS) (Ramsøy and Overgaard, 2004]. The task difficulty was manipulated by altering the contrast of the stimuli according to a 2-up-1 down staircase function. This allowed for estimations of the impact of dopamine on perceptual awareness (changes in the proportion of trials on which awareness was reported), and objective performance [Rounis et al., 2010].

In Experiment 2, a separate group of participants rated how well adjectives described themselves and the Danish Queen respectively, and again half of the participants were given Sinemet and the other half placebo. In this experiment, participants were subsequently asked to recollect whether they had previously described an adjective as fitting themselves (task 1: self) or the Queen (task 2: other). A third, online, task without a memory component was performed in which the participants counted the number of syllables of each adjective presented online (task 3: syllables) (Fig. 2a). This part permitted estimation of dopaminergic influence on self-awareness extended in time using introspection (autonoetic metacognition, see Frith, 2012; Metcalfe and Son, 2012]. Simultaneous MEG recordings were used to investigate corresponding activity in the main cortical regions of the paralimbic network; medial prefrontal cortex, PCC, and a control region (right visual area V1) (Fig. 2b). MEG offers a high temporal resolution in combination with a decent spatial resolution even in deeper cortical and paralimbic regions. However, the

spatial resolution declines with increased distance from the sensors [Gross et al., 2003]. For this reason we did not include measurements from the thalamus or striatum in the present work.

METHODS

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (De Videnskabsetiske Komitéer for Region Midtjylland) and the Center for Functionally Integrative Neuroscience Research Board.

Participants and Procedures

Experiment 1: Minimal self-awareness

Eighty right-handed young males, without a history of diseases or drugs affecting the brain, participated in the study. Only males were included as the female menstrual cycle may influence the dopamine response.

The participants were randomly distributed to two age-matched groups. One group of 40 persons was given placebo capsules containing starch only, and another group of 40 persons was given capsules containing Sinemet (100 mg L-dopa mixed with 25 mg carbidopa to inhibit peripheral metabolism of L-dopa and minimize peripheral side effects). This medication is commonly used to treat Parkinson's disease. The capsules were visually identical and the experiment was double-blinded: neither the participant nor the experimenters were aware of the group. The physician administering the capsules was aware of the content, but was not involved in giving participant instructions. This allowed for estimation of the impact of dopamine on perceptual awareness.

Of the initial group of participants, three were excluded prior to data inspection due to side effects from the Sinemet (nausea), misunderstanding the task, or dyslexia. Upon data inspection, three additional participants were excluded as their staircase function used to regulate the task difficulty did not converge (they had fewer than ten reversals). It was verified that the groups remained age-matched [$t(72) = -1.1595$, $P = 0.2501$], with 36 persons remaining in the dopamine group (mean age 23.4, SD = 2.7) and 38 persons remaining in the placebo group (mean age 24.2, SD = 3.2).

In the experiment, the participants had to detect a briefly presented and masked trait adjective and select the correct word among two possible answers (Fig. 1). Several days prior to the study, participants rated how well each of 377 trait adjectives (subset of Anderson, 1968] described themselves and another person known to all participants: the Danish Queen. This was done using a four-point scale (1: does not match at all, 2: matches poorly, 3: matches reasonably well, 4: matches absolutely). The experiment consisted of two tasks, referred to as "self" and "other." In the self-task, the participant had to identify words previously described as fitting himself and in the other-task, the participant had to identify words previously described as fitting the Queen. Following the discrimination, the participant rated the level of awareness based on the four-point Perception Awareness Scale (1: no perception of a word, 2: a brief flash of a word, 3: an almost clear perception, 4: a clear perception) (Ramsøy and Overgaard, 2004; Sandberg et al., 2010]. The two tasks were presented in blocks of five trials (randomized block order), with a preceding text informing the participant of the upcoming condition, for example, "You have previously rated the following words to fit the Danish Queen." There was no overlap between the target words in the self and other task, nor with the forced-choice alternative words (words that the participant had previously marked as fitting both himself and the Queen). Each word was used twice and each participant had an individual number of trials based on their prior word rating (mean number of trials 77.9, SD = 17.4). The forced choice alternatives were matched on length to the target words. The stimulus duration was fixed at 33 ms, and the task difficulty was controlled by modifying the contrast of the presented word, using a two-up-one-down staircase function [Cornsweet, 1962; Watson and Pelli, 1983] enforcing an accuracy approximating 70.7%. Prior to the main study, a 5–10 min training round was used to acquaint the participant with the paradigm and to determine the initial contrast level. The training consisted of adjectives not used in the main task.

The paradigm was implemented using the Python-based package PsychoPy [Peirce, 2008] (version 1.77) on an Intel Quad-core computer (2.66 GHz, 3.25 GB memory) running Windows XP and presented on a 19-inch screen (1024 × 768 resolution, 32 bit color depth, 60 Hz refresh rate). It was verified that the presentation times were exact within one millisecond using an oscilloscope and a photo sensor. The experiment took place in a single-person test room, where the light was kept dimmed (constant across all participants) and external noise reduced.

Experiment 2: Extended self-awareness

Forty-two right handed male participants, without a history of diseases or drugs affecting the brain, participated in the study. Two participants were excluded, one due to side effects from the Sinemet (nausea) and one who had misunderstood the task. The participants were randomly distributed to two age-matched groups [$t(38) = 0.4577$, $P = 0.65$]. One group was given 125 mg of Sinemet (mean age 27.2, SD = 5.8), and another group was given a placebo capsule (mean age 26.4, SD = 5.6).

For each word, participants performed one of three tasks, one related to retrieval of self-related judgments, one related to retrieval of other-related judgments, and a control task during which participants simply reported whether a presented adjective had an even or odd number of syllables. The series were presented in counter-balanced order. The tasks were referred to as "self," "other," and

"syllables" (Fig. 2a). In "self" the participant first rated how well a given adjective fitted his own personality on a four-point scale identical to the one described in Experiment 1. Adjectives were presented consecutively on a screen. The series of adjectives was subsequently repeated in pseudorandom order ensuring that any word was on average shown again 5 min later. During the repetition, the participant was required to retrieve his previous judgment on a two-point scale (word previously judged as "fitting" vs. not fitting) (Fig. 2a). The changes in presentation order and required response were introduced to avoid automatic motor responses. A total of 360 trait adjectives [Anderson, 1968] were used for each participant, with 40 words in each combination of block and task (matched on likeableness, word frequency, word length and number of vowels).

Stimulus words were selected from a list of 555 personality-trait adjectives [Anderson, 1968] that were translated into Danish, as no similar Danish ranking exists. Of the full word list, the 360 most frequent Danish adjectives were identified using a Danish corpus (www.ordnet.dk/korpusdk), and the words were pseudorandomly divided into nine-word lists based on the English likeableness rating, the Danish word frequency, the number of characters and the number of vowels. The randomization was repeated until a one-way ANOVA on each score showed no significant differences between the word lists (likeableness, $P = 0.96$, frequency, $P = 0.95$, word length, $P = 0.99$, and number of vowels, $P = 0.99$). The paradigm was implemented in E-prime (www.pstnet.com/eprime.cfm), version 2.0. It was run on a desktop computer (Dell Optiplex 780, 1024 × 768 resolution, 32 bit color depth, 60 Hz refresh rate) and was projected on to a back-projection screen in the shielded room (using a Panasonic PT-D10000E projector). The reflective screen was located approximately 1 m from the participant and all participants concurred that they could read the text.

MEG Recording and Analysis

In Experiment 2, MEG was recorded throughout the paradigm. The MEG analysis was performed on the data recorded during retrieval of episodic memory to obtain a measure of extended (or narrative) self-awareness, and during performance of syllable calculations online. Unlike electroencephalography (EEG) and magnetic resonance imaging (MRI), MEG allows the study of paralimbic regional activity and interaction on a millisecond timescale and with decent spatial resolution. Here we measured regional power in two main nodes of the paralimbic network of self-awareness, medial prefrontal cortex and PCC, and in a control region, right primary visual cortex (rV1) (Fig. 2b). The network was identified in a previous PET study of hemodynamic paralimbic interactions elicited by extended self-reference [Lou et al., 2004]. Midline Talairach coordinates of medial prefrontal and posterior cingulate/medial parietal were measured for identification of targets for the MEG analysis used in the present study (0, 59, 40; 0, –50, 28; and 0, –38, 8, respectively). The control region was chosen because this region is anatomically and functionally comparatively separate from the midline regions investigated.

Communication between regions was investigated by Granger causality in order to test if it was dependent of frequency, medication, or whether the interaction between medial prefrontal cortex and PCC was different from interaction between medial prefrontal cortex and the control region rV1.

The MEG data were recorded using a TRIUX MEG system (Elekta Instruments AB, Stockholm, Sweden) with 204 planar gradiometers and 102 magnetometers; electromagnetic recordings were sampled at 1 kHz using analog filtering of 0.1–330 Hz. Horizontal and vertical eye movements were recorded bipolarly using surface electrodes, and a continuous measure of the head position in the scanner was obtained using five head coils. The data were coregistered to individual magnetic resonance (MR) images by registering three landmark points recognizable on the MR in addition to 50+ points marking the head shape. The structural MR was acquired in a separate session on a Siemens 3T MR scanner with a resolution of 1 × 1 × 1 mm.

Using Elekta's MaxFilter software (Version 2.1), the head position was transformed to the one initially recorded. Electromagnetic sources external to the participant's head were suppressed based on Maxwell's equations and, in addition, sources in the boundary region were projected out using a temporal extension of the Signal Space Separation method. A log of the head movement was inspected, while blinded to the task and medication. A total of two data blocks (of 120 trials each) were removed in this process due to excessive movement or faulty recording of head position. The results of the MaxFiltering were visually inspected, and artifact-inducing channels were excluded in an iterative manner. In the remaining analysis, only planar gradiometers were used. Using principal component analysis, the dimension of the data was reduced to 64 components. Subsequent independent component analysis (ICA) was used to project out electrooculography (eye movement), electrocardiography (heartbeat) artifacts, and flux jumps on sensors. Visual inspection of all the data verified that this was done successfully. The data were epoched into the three tasks (self, other, syl) with a trial defined as −1000 to 3000 ms relative to the word onset. The variance of the individual trials was inspected and trials with excessive variance were excluded, based on visual inspection while blinded to the task and group.

Using FieldTrip [Oostenveld et al., 2011], the head shape was extracted and linearly normalized to a Montreal Neurological Institute (MNI) template in order to generate a single-shell forward model. This was corrected using the previously found ICA weights to account for projecting out

mostly frontal components. With a spatial filter, data were projected into the brain and time series were extracted from the prespecified regions of interest (ROIs) for each participant (medial prefrontal cortex, PCC and rV1).

As Granger causality is sensitive to band-pass filtering and the sample rate of the data, and to ensure stationarity, the approach from [Barnett and Seth, 2011] was used. The data were downsampled to 256 Hz and the beamformer was used to extract time series for the individual frequencies of interest. With Granger causality, an autoregressive model of a time series is created, by estimating future values as a weighted sum of present and previous values. If the model error of a region A is significantly reduced by including present or previous values from a different region B, then region B is said to Granger-cause region A. Granger-causality was analyzed using the GCCA toolbox [Seth, 2010]. The model order (number of previous samples included in the model) was initially sought estimated using the Akaike information criterion (AIC) [Akaike, 1974] and Bayesian information criterion (BIC) [Schwarz, 1978] criteria. Neither of these methods converged, as the fitting parameter (which was sought minimized) kept decreasing with increasing model order. This was despite the penalty term in the model, which penalized model complexity. The problem of estimating the model order is common in Granger Causality estimates of EEG/MEG source data (see Barrett et al., 2012; Gow et al., 2008]. A model order of five was chosen as this is sufficient to account for the propagation delay between the ROI. It was verified that results were robust for model orders in the range of 5–20.

Statistics

The R statistical software [R Core Team, 2013] was used for all statistical analysis.

Experiment 1: With the staircase function used to regulate the trial difficulty the contrast level of the individual trials were tightly bound. To model this dependency, a Markov model was applied. Stationary distributions [Hastings, 1970] were estimated for each subject using a maximum-likelihood estimate. Stationary distributions reflect the probability of each contrast-level for a randomly selected trial X. We could thus obtain a summary statistic of the (Markov-estimated) average contrast-level for each participant by summing the products of the probability for each contrast-level and the corresponding contrast-value. The Markov estimates were made using the "markovchain" package [Spedicato, 2014].

Metacognition was modeled using generalized linear mixed effects regression using a binomial distribution (as implemented in R-function glmer, Bates et al., 2014]. In modeling of metacognition it was verified that the described model performed significantly better than a model that did not include any interaction between awareness and medication ($P = 0.0289$).

Experiment 2: Only retrieval trials (self/other) and syllable trials (syl) were used for the analysis, that is, encoding trials were not used. In the analysis of the behavioral data it was verified that the model was significantly better at modeling the data than a null model ($P = 0.028$).

For the medial prefrontal cortex power findings, it was verified that the model performed significantly better than a corresponding null-model ($P = 0.027$). For the whole-brain beamforming, the power (during the 1 s after word onset) was calculated for each voxel and averaged over trials for each participant (and task). A Monte Carlo simulation with 1000 randomizations of the unpaired *t*-test was used to estimate the Z-score for each voxel, when comparing participants given placebo and those given Sinemet. No correction for multiple comparisons was applied in the whole-head analysis.

RESULTS

Experiment 1: Minimal Self-Awareness with Noetic Metacognition

Task difficulty was regulated by increasing and decreasing the contrast of the stimuli to enforce a theoretical accuracy of 70.7% on both self-task and other-task. Despite this staircasing procedure, the accuracy in the dopamine group was significantly higher than accuracy in the placebo group (Wilcoxon rank sum test: $W = 860$, $P = 0.031$), while no difference in task (self/other) accuracy was found (Wilcoxon signed rank test: $V = 1491$, $P = 0.432$). Using contrast as a measure of task difficulty, we modeled Markov-estimated average contrast level as a linear response of task (self/other), medication (dopamine/placebo), and the interaction between them. An ANOVA revealed no significant effects [F's(1,136) < 1.2, P 0.25 for all comparisons]. PAS ratings were split in two categories: no awareness (PAS response 1) and awareness (PAS response 2–4). Perceptual awareness was examined using logistic regression (Fixed effects: task and medication. Random effect: participant), and a significant main effect of task was found with higher awareness of self-related, compared to other-related words (z=–5.4, $P < 0.001$). No significant main effect of medication was found, and no significant interactions were found ($z < 1$ for all comparisons).

Noetic metacognition was examined using logistic regression with the forced choice response (correct/incorrect) as the dependent variable (Fixed effects: awareness, medication, task, awareness × task interaction, and awareness × medication interaction. Random effect: participant). The model revealed significantly improved accuracy for self-reference as well as other-reference during subjective awareness, and also improved interaction between medication and awareness, where medication increased the difference in accuracy between aware and unaware trials ($z = 2.2$, $P = 0.029$) respectively (Fig. 3). No three-way interaction was found between task, medication and awareness ($z = –0.55$, $P = 0.585$).

Trait adjectives used in the self-task were on average more likeable than those used to describe the Queen, but by including likeability as a covariate no change was seen (Supporting Information).

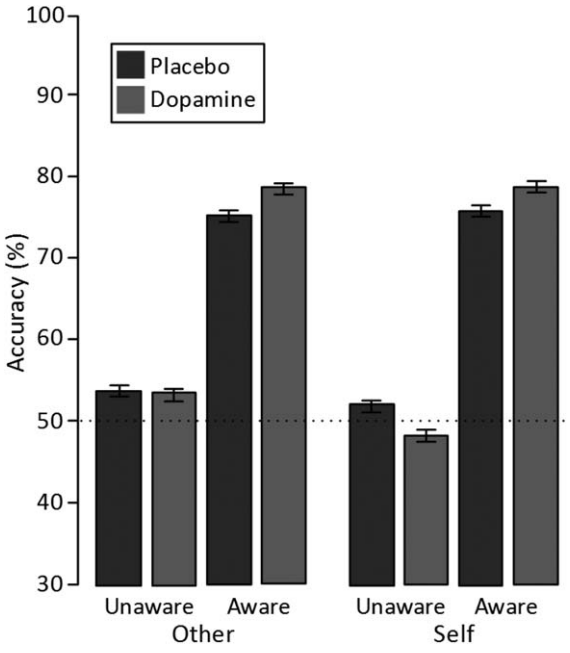

Figure 3.

Effect of dopamine on noetic metacognition (Experiment 1). Awareness of meaningful stimuli was, as expected, linked to higher degree of accuracy in forced choice task. This occurred whether the adjectives were explicitly self-referent or other-referent (minimal self-awareness). The effect was significantly enhanced with dopamine, demonstrating increased noetic metacognition [Metcalfe and Son, 2012]. (Estimates from a logistic regression on accuracy with task, medication, and awareness as independent variables, Error bars illustrate the 95%-confidence intervals).

We aimed at testing the hypothesis that dopaminergic stimulation increases the accuracy for a given degree of awareness, or, in other words, that the subjective experience of awareness became a better predictor of performance (noetic metacognition) with dopamine. This was indeed confirmed. A more complex signal-detection oriented approach to analysis could have been chosen as an alternative. We did attempt this but failed. (see Supporting Information for details). Our technique using random effects has the advantage of naturally handling repeated measures, as well as allowing standard testing of regression/ANOVA type structures for the independent variables and their interaction.

The main finding of this experiment was thus a general increase in noetic metacognition [Frith, 2012; Metcalfe and Son, 2012] caused by dopamine.

Experiment 2: Extended Self-Awareness with Autonoetic Metacognition in Explicit Self-Reference

For the behavioral part, we used logistic regression in a mixed model with response (correct/incorrect) as the dependent variable (Fixed effects: medication and task. Random effect: participant). A main effect of task was found, with fewer errors during the self-task than the other-task (z=–3.46, $P < 0.001$). A trend for a main effect of dopamine was also demonstrated ($z = 1.88$, $P = 0.067$). There was a significant interaction between task and medication ($z = –2.68$, $P = 0.007$). Here, dopamine improved the performance in the self-task more than in the other-task (Fig. 4a). Concomitantly, there was an increase in MEG power across all frequency bands in the 5–100 Hz range in the medial prefrontal cortex (Fig. 4b).

To test if the selectivity of the dopaminergic effect on the self-task could be due to preferential power increase in the medial prefrontal region known to selectively instrumental in self-evaluation [Luber et al., 2012], we did the following analyses: (1) Separate analysis of medial prefrontal cortex and PCC, which showed that dopaminergic stimulation significantly increased MEG power in the medial prefrontal region (linear mixed effect model. Fixed effect: medication. Random effect: participant: $t = 2.231$, $P = 0.026$), while power was unchanged in the PCC region and right V1. (2) Whole head mapping of dopamine-induced power, which showed an increase in the gamma frequency range (30–100 Hz), and Z-scores revealed that the increase was maximal (more than 50%) and significant ($P < 0.05$, uncorrected, Monte Carlo simulation of independent t-test) throughout the medial prefrontal region (Fig. 5). Having demonstrated significantly increased gamma power in the medial prefrontal region, and not in the posterior region, we wished to visualize a posterior–anterior trend of dopaminergic effect on gamma power consonant with the gradient in dopaminergic D1 and D2 receptor concentration [Ko and Strafella, 2012; Lidow et al., 1991] The results are shown in Figure 5, confirming our hypothesis of preferential dopamine induced power increase in medial prefrontal cortex by showing that the effect of power is only seen in that region ($Z > 2$, uncorrected, deemed adequate for further supporting our hypothesis). There appeared to be one possible exception, namely the suggestion that dopaminerergic activation may also increase gamma power in the right insula. This could, however, not be concluded from the present study, as correction for multiple comparisons was required in this case being not included in our hypothesis. No cortical region fulfilled that criterion.

A Granger Causality computation showed that the interaction between medial prefrontal cortex and PCC was stronger in gamma frequency band (30–100Hz) than in lower frequency bands (5–30Hz) (Mixed effect model with direction and frequency as main effects and medication, id and trial as nested random effects, $t = 59.58$. Including frequency as main effect significantly improved the model $\chi^2(1) = 3509.1$, $P < 0.0001$).

The main findings in Experiment 2 were thus a dopamine-induced improved explicit self-awareness with introspection (autonoetic metacognition), and a

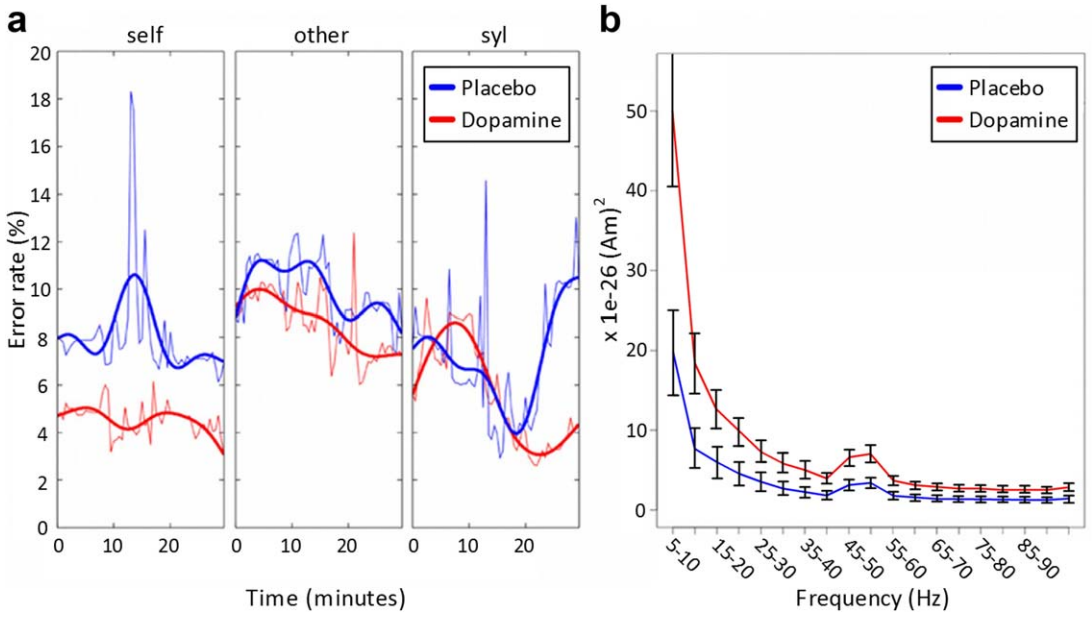

Figure 4.

Effect of dopamine on explicit self-referent extended self-awareness and autonoetic metacognition (Experiment 2). (**a**) Dopamine caused a significant decrease in error rates for the "self" condition. Average error rates across participants calculated within a 15 min window shifted by 30 s (window centered so a given value in the plot is an average of responses within ± 7.5 min). The plot covers the time interval with data from all participants. (**b**) Medial prefrontal cortex power increased by dopamine across all three experimental tasks and all frequency bands between 5 and 100Hz, demonstrating increased autonoetic metacognition [Metcalfe and Son, 2012].

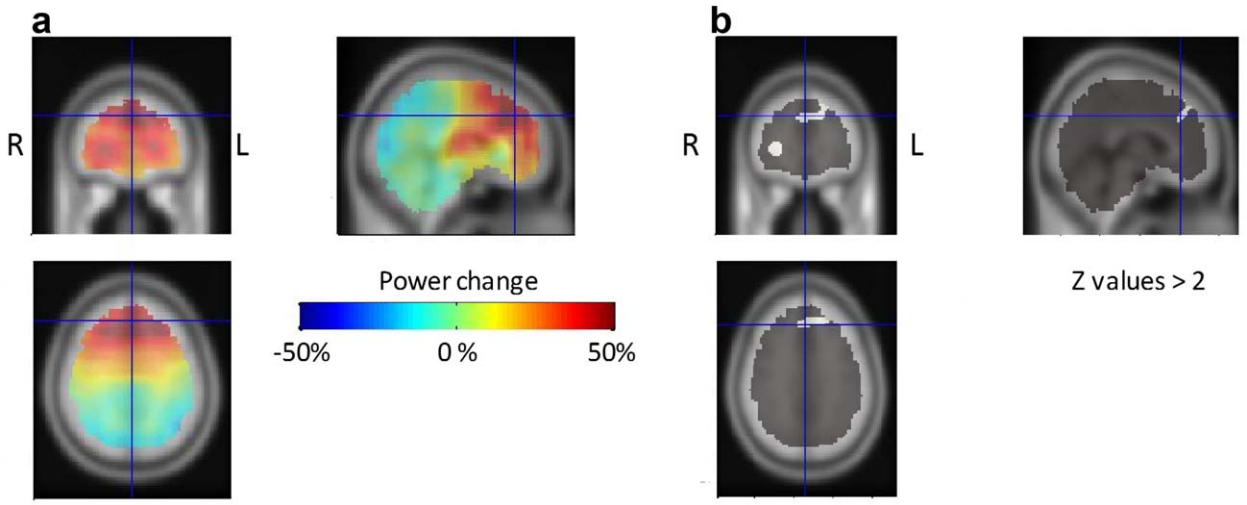

Figure 5.

Distribution of MEG power differences between dopamine and placebo groups. (**a**) Increase in power occurs mainly in the medial prefrontal cortex. The blue cross marks peak location with 56% increase at the MNI-coordinate (0, 36, 36) mm corresponding to the frontal superior medial region (Found using AAL atlas, see Tzourio-Mazoyer et al., 2002]. (**b**) values *Z*-values >2 from Monte Carlo simulation of the difference between the placebo and dopamine group. The slices and blue crosses are identical to the power plot.

concomitant preferential power increase in medial prefrontal cortex in the gamma range.

DISCUSSION

Overall, the present results demonstrate dopaminergic regulation of conscious metacognition (self-monitoring). In experiment 1, dopamine increased the general noetic [Metcalfe and Son, 2012] metacognitive capacity of the participants. Metacognitive capacity, in this context, was defined as the meaningfulness of awareness responses and operationalized as the relationship between correct responses and reports of the degree of awareness [Rounis et al., 2010]. The effect was seen in both categories of adjectives, whether explicitly related to the self or other. This indicates a general effect on noetic metacognition, as all stimuli were implicitly relevant to the self by constructing meaningful words (i.e., minimal self-awareness) [Kjaer et al., 2001; Lou et al., 2011c]. In Experiment 2, self-awareness, as evidenced by correct retrieval of self-judgments, was increased by dopaminergic stimulation (autonoetic metacognition, Metcalfe and Son, 2012]. Maximal electromagnetic effect of dopaminergic stimulation was seen in the medial prefrontal cortex independent on task, in agreement with the cortical distribution of dopaminergic receptors [Ko and Strafella, 2012; Lidow et al., 1991]. Given that electromagnetic activity specifically in medial prefrontal cortex is instrumental in self-evaluation [Luber et al., 2012], this specific distribution of dopamine effect on power explains its specific effect on extended self-awareness. While several electrophysiological and volumetric studies have found that first-order perceptual awareness correlates primarily with ventral stream activity in the visual and temporal cortices [Fleming et al., 2010; Koivisto and Revonsuo, 2010; Petrides and Pandya, 2007; Sandberg et al., 2013], one study using Transcranial magnetic stimulation (TMS) has found dorsolateral prefrontal cortex to be instrumental in metacognition [Rounis et al., 2010]. Interestingly, dorsolateral prefrontal activity is tightly linked to regulation of dopamine release in the medial prefrontal and orbitofrontal cortex (OFC) in several human and animal studies. The impact on metacognition of TMS over this area by may therefore have been a direct modulation of the adjacent medial prefrontal region.

The effect of dopamine on noetic metacognition and extended self-awareness with autonoetic metacognition may, hypothetically, be linked to other functions associated with the medial prefrontal region. Dopaminergic stimulation is, for instance, known to improve motivation to obtain rewards in animals [Berridge and Kringelbach, 2008; Ward et al., 2012] and humans [Wardle et al., 2011] by stimulating a neural system that attributes incentive salience to reward cues. This system primarily consists of mesocorticolimbic dopaminergic neurons that connect the ventral tegmental area with the nucleus accumbens, neostriatum, amygdala, ventral pallidum and prefrontal cortex [Robinson et al., 2013]. A main function of this system is to transform ordinary stimuli, such as cues associated with rewards, into incentive stimuli, that is, making them 'attractive' and able to trigger an urge to pursue and consume their reward [Robinson et al., 2013].

A link between subjective awareness and reward would be expected if the main cognitive function of awareness is to make adaptive control of behavior possible, a widely held belief [Cleeremans, 2011]. Expectation of reward therefore predicts both awareness and performance. A link between reward and awareness is further suggested by the overlap between the paralimbic reward system and the paralimbic network of self-awareness, since both include orbito-frontal, medial prefrontal, posterior cingulate/medial parietal regions and striatum [Kjaer et al., 2001, 2002b; Liu et al., 2011; Lou et al., 2004; Newen and Vogeley, 2003]. Also direct evidence has demonstrated the link between reward maximization and human detection behavior and confidence, with confidence used as a measure of awareness [Navalpakkam et al., 2009]. The primary function of medial prefrontal cortex in the regulation of the paralimbic network is also consistent with its role in metacognition [Amodio and Frith, 2006; Frith, 2012].

A close association between the networks of mood and conscious experience has been demonstrated in both psychophysical studies [Barros et al., 2001; Wise and Bozarth, 1985] and by their common local field potentials obtained from the anterior cingulate cortex with an electrode implanted for deep brain stimulation therapy [Rømer Thomsen et al., 2011]. The close interaction between reward and conscious experience is also supported by behavioral findings of improved conscious reportability with positive compared to negative and neutral stimuli [Rømer Thomsen et al., 2011]. It is interesting that dopamine and the neuropeptide oxytocin have been shown to interact in reward processing in rodents [Baracz and Cornish, 2013] and that oxytocin influences centro-frontal event potentials elicited by judgment of personal traits of oneself differently from a control person, suggesting oxytocin influence on self-awareness [Liu et al., 2013].

There are other hypothetical possibilities which should also be taken into account. Dopamine has consistently been shown to improve working memory [e.g., Moran et al., 2011]. Recently, it has been demonstrated that episodic memory that persists for several hours is modulated by dopamine, possibly due to dopamine activation of hippocampal protein synthesis [Chowdhury et al., 2012]. Therefore, working memory enhancement could hypothetically offer an explanation of the effect of dopaminergic stimulation on self-awareness. However, it is difficult to see how this would explain the effect on retrieval of self-judgment but not other-judgment.

With respect to the possible involvement of attention in regulation of self-awareness, it is important to realize that in order to have an effect on conscious experience, dopaminergic release must occur early in sensory processing [Lou et al., 2011c]. This has been demonstrated in a series of

investigations: The midbrain superior colliculus is a primary visual structure, specialized for the detection of rewarding [Comoli et al., 2003], unexpected [Dommett et al., 2005], and salient visual stimuli [Redgrave et al., 1999]. It is reached directly by visual pathways and has direct connections to the substantia nigra pars compacta, the origin of nigrostriatal fibers innervating the striatum and limbic structures [Dommett et al., 2005]. The latency of this circuitry is very short, approximately 100 ms. In this time, dopaminergic neurons respond to a salient visual event even before the onset of a visual saccade, and before the stimulus is in focus [Redgrave et al., 1999]. The effect of the activity in the circuitry is therefore pre-attentive. In other words: Salience and conscious experience precedes attention.

Present literature indicates that self-awareness is linked not only to activity in medial prefrontal/anterior cingulate cortex (for review, see Amodio and Frith, 2006] but also to activity in precuneus/medial parietal cortex and adjacent paralimbic structures [Cavanna and Trimble, 2006; Lou et al., 2011b]. This paralimbic network of self-awareness is often termed "default mode network" due to the fact that its activity is reduced when focusing on external events [Raichle et al., 2001].

TMS has shown that this region is instrumental in self-enhancement processing, that is the preference of processing self-related stimuli and memories when compared to other [Luber et al., 2012]. While self-processing is specifically reduced with TMS in these experiments targeting the medial prefrontal region specifically, we have shown in the present Experiment 2 that stimulating this region with dopamine results in specific enhancement of self-processing when compared to the processing of other.

In other words, it has now been established that self-processing in the medial pre-frontal region may be either reduced or enhanced by electromagnetic or molecular manipulation. Furthermore, the granger causality analysis shows a causal interaction between the medial prefrontal region and the posterior cingulate/medial parietal region, the latter being instrumental in retrieval of self-related information [Lou et al., 2004].

CONCLUSION

Dopamine improved the prediction by subjective awareness of objective performance in an online task with minimal self-awareness (noetic metacognition). Dopamine also enhanced extended self-awareness with introspection (autonoetic metacognition) concomitant with stimulation of the anterior cingulate/prefrontal cortex, a process which seems to be tightly linked to incentive stimulation and reward. We speculate that this mechanism may be fundamental for optimal resource allocation not only for the individual, but also in its interaction with others, as reportablity is inherent in the way awareness is operationalized [e.g., Lou et al., 2011c; Rømer Thomsen et al., 2011].

Given the prevalence and severity of disorders of conscious self-monitoring, like addiction, ADHD, autism, borderline personality disorder, and so on, it is of prime importance to understand the pathophysiology. The discovery of dopaminergic regulation of self-awareness indicates the possibility of pharmacological treatment and up-regulation of dopaminergic receptors by training [e.g., McNab et al., 2009] not only in ADHD, but also in the related disorders.

ACKNOWLEDGMENTS

No novel drugs have been used in the study. We thank Vagn Andersen and Jean Pierre Changeux for comments on the manuscript, Christopher Bailey for scientific and technical support, and Henriette Vuust for help with figures.

AUTHOR CONTRIBUTIONS

The study was conceived by H.C.L.; Experiment 1 was designed by KS, LMA and M.J.; Experiment 2 was designed by H.C.L., M.J., and K.R.T.; screening interviews and selection of participants were done by K.R.T., M.J., and H.C.L.; pharmacological intervention by H.C.L.; MEG data acquisition by M.J., and K.R.T.; analysis of MEG by M.J. and J.G.; statistical analysis of study 1 by L.M.A., M.J., and K.M.; statistical analysis of study 2 by M.J., J.G., and K.M.; the manuscript was written by H.C.L., M.J., K.R.T., and K.S. All authors contributed to the manuscript and data analysis. The authors declare no conflict of interest.

REFERENCES

Akaike H (1974): A new look at the statistical model identification. IEEE Trans Automatic Control 19:716–723.

Amodio DM, Frith CD (2006): Meeting of minds: The medial frontal cortex and social cognition. Nat Rev Neurosci 7:268–277.

Anderson NH (1968): Likableness ratings of 555 personality-trait words. J Pers Soc Psychol 9:272–279.

Baracz SJ, Cornish JL (2013): Oxytocin modulates dopamine-mediated reward in the rat subthalamic nucleus. Horm Behav 63:370–375.

Barnett L, Seth AK (2011): Behaviour of Granger causality under filtering: Theoretical invariance and practical application. J Neurosci Methods 201:404–419.

Barrett AB, Murphy M, Bruno MA, Noirhomme Q, Boly M, Laureys S, Seth AK (2012): Granger causality analysis of steady-state electroencephalographic signals during propofol-induced anaesthesia. PLoS One 7:e29072.

Barros DM, Mello e Souza T, De David T, Choi H, Aguzzoli A, Madche C, Ardenghi P, Medina JH, Izquierdo I (2001): Simultaneous modulation of retrieval by dopaminergic D(1), beta-noradrenergic, serotonergic-1A and cholinergic muscarinic receptors in cortical structures of the rat. Behav Brain Res 124: 1–7.

Bates D, Maechler M, Bolker B, Walker S (2014): lme4: Linear mixed-effects models using Eigen and S4. R package version 1.1-7, http://cran.r-project.org/web/packages/lme4

Bechara A (2005): Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. Nat Neurosci 8:1458–1463.

Berridge KC, Kringelbach ML (2008): Affective neuroscience of pleasure: Reward in humans and animals. Psychopharmacology (Berl) 199:457–480.

Cavanna AE, Trimble MR (2006): The precuneus: A review of its functional anatomy and behavioural correlates. Brain 129(Pt 3): 564–583.

Chowdhury R, Guitart-Masip M, Bunzeck N, Dolan RJ, Duzel E (2012): Dopamine modulates episodic memory persistence in old age. J Neurosci 32:14193–14204.

Cleeremans A (2011): The radical plasticity thesis: How the brain learns to be conscious. Front Psychol 2:86.

Comoli E, Coizet V, Boyes J, Bolam JP, Canteras NS, Quirk RH, Overton PG, Redgrave P (2003): A direct projection from superior colliculus to substantia nigra for detecting salient visual events. Nat Neurosci 6:974–980.

Cornsweet TN (1962): The staircase-method in psychophysics. Am J Psychol 75:485–491.

Dommett E, Coizet V, Blaha CD, Martindale J, Lefebvre V, Walton N, Mayhew JE, Overton PG, Redgrave P (2005): How visual stimuli activate dopaminergic neurons at short latency. Science 307:1476–1479.

Fleming SM, Weil RS, Nagy Z, Dolan RJ, Rees G (2010): Relating introspective accuracy to individual differences in brain structure. Science 329:1541–1543.

Frith CD (2012): The role of metacognition in human social interactions. Philos Trans R Soc Lond B Biol Sci 367:2213–2223.

Gallagher S (2000): Philosophical conceptions of the self: Implications for cognitive science. Trends Cogn Sci 4:14–21.

Gow DW, Jr., Segawa JA, Ahlfors SP, Lin FH (2008): Lexical influences on speech perception: A Granger causality analysis of MEG and EEG source estimates. Neuroimage 43:614–623.

Gross J, Timmermann L, Kujala J, Salmelin R, Schnitzler A (2003): Properties of MEG tomographic maps obtained with spatial filtering. NeuroImage 19:1329–1336.

Hastings WK (1970): Monte Carlo sampling methods using Markov chains and their applications. Biometrika 57:97–109.

Ingvar DH (1985): "Memory of the future": An essay on the temporal organization of conscious awareness. Hum Neurobiol 4: 127–136.

Kjaer TW, Nowak M, Kjaer KW, Lou AR, Lou HC (2001): Precuneus-prefrontal activity during awareness of visual verbal stimuli. Conscious Cogn 10:356–365.

Kjaer TW, Bertelsen C, Piccini P, Brooks D, Alving J, Lou HC (2002a): Increased dopamine tone during meditation-induced change of consciousness. Cogn Brain Res 13:255–259.

Kjaer TW, Nowak M, Lou HC (2002b): Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. NeuroImage 17:1080–1086.

Ko JH, Strafella AP (2012): Dopaminergic neurotransmission in the human brain: New lessons from perturbation and imaging. Neuroscientist 18:149–168.

Koivisto M, Revonsuo A (2010): Event-related brain potential correlates of visual awareness. Neurosci Biobehav Rev 34:922–934.

Kwan VS, Barrios V, Ganis G, Gorman J, Lange C, Kumar M, Shepard A, Keenan JP (2007): Assessing the neural correlates of self-enhancement bias: A transcranial magnetic stimulation study. Exp Brain Res 182:379–385.

Lidow MS, Goldman-Rakic PS, Gallager DW, Rakic P (1991): Distribution of dopaminergic receptors in the primate cerebral cortex: Quantitative autoradiographic analysis using [3H]raclopride, [3H]spiperone and [3H]SCH23390. Neuroscience 40:657–671.

Liu X, Hairston J, Schrier M, Fan J (2011): Common and distinct networks underlying reward valence and processing stages: A meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev 35:1219–1236.

Liu Y, Sheng F, Woodcock KA, Han S (2013): Oxytocin effects on neural correlates of self-referential processing. Biol Psychol 94: 380–387.

Lou HC, Luber B, Crupain M, Keenan JP, Nowak M, Kjaer TW, Sackeim HA, Lisanby SH (2004): Parietal cortex and representation of the mental Self. Proc Natl Acad Sci USA 101:6827–6832.

Lou HC, Gross J, Biermann-Ruben K, Kjaer TW, Schnitzler A (2010): Coherence in consciousness: Paralimbic gamma synchrony of self-reference links conscious experiences. Hum Brain Mapp 31:185–192.

Lou HC, Joensson M, Biermann-Ruben K, Schnitzler A, Ostergaard L, Kjaer TW, Gross J (2011a): Recurrent activity in higher order, modality non-specific brain regions: A Granger causality analysis of autobiographic memory retrieval. PLoS One 6:e22286.

Lou HC, Joensson M, Kringelbach ML (2011b): Yoga lessons for consciousness research: A paralimbic network balancing brain resource allocation. Front Psychol 2:366.

Lou HC, Skewes JC, Thomsen KR, Overgaard M, Lau HC, Mouridsen K, Roepstorff A (2011c): Dopaminergic stimulation enhances confidence and accuracy in seeing rapidly presented words. J Vis 11:1–6.

Luber B, Lou HC, Keenan JP, Lisanby SH (2012): Self-enhancement processing in the default network: A single-pulse TMS study. Exp Brain Res 223:177–187.

McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, Forssberg H, Klingberg T (2009): Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science 323:800–802.

Metcalfe J, Son LK (2012): Anoetic, noetic, and autonoetic metacognition. In: Michael JB, Josef P, Joëlle P, editor. In Foundations of Metacognition. Oxford: Oxford University Press.

Moran RJ, Symmonds M, Stephan KE, Friston KJ, Dolan RJ (2011): An in vivo assay of synaptic function mediating human cognition. Curr Biol 21:1320–1325.

Navalpakkam V, Koch C, Perona P (2009): Homo economicus in visual search. J Vis 9:311–316.

Newen A, Vogeley K (2003): Self-representation: Searching for a neural signature of self-consciousness. Consci Cogn 12:529–543.

Oostenveld R, Fries P, Maris E, Schoffelen JM (2011): FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011:156869.

Peirce JW (2008): Generating Stimuli for Neuroscience Using PsychoPy. Front Neuroinform 2:10.

Petrides M, Pandya DN (2007): Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J Neurosci 27:11573–11586.

R Core Team (2013): R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. Proc Natl Acad Sci USA 98:676–682.

Ramsøy TZ, Overgaard M (2004): Introspection and subliminal perception. Phenomenol Cogn Sci 3:1–23.

Redgrave P, Prescott TJ, Gurney K (1999): Is the short-latency dopamine response too short to signal reward error? Trends Neurosci 22:146–151.

Robinson MJF, Robinson TE, Berridge KC (2013): Incentive Salience and the Transition to Addiction. In: Miller, P. (Ed.), Biological Research on Addiction. Academic Press, San Diego, USA, pp 391–399.

Rømer Thomsen K, Lou HC, Joensson M, Hyam JA, Holland P, Parsons CE, Young KS, Moller A, Stein A, Green AL, Kringelbach ML, Aziz TZ. (2011): Impact of emotion on consciousness: positive stimuli enhance conscious reportability. PLoS One 6: e18686.

Rømer Thomsen K, Joensson M, Lou HC, Moller A, Gross J, Kringelbach ML, Changeux JP (2013): Altered paralimbic interaction in behavioral addiction. Proc Natl Acad Sci USA 110: 4744–4749.

Rounis E, Maniscalco B, Rothwell JC, Passingham RE, Lau H (2010): Theta-burst transcranial magnetic stimulation to the prefrontal cortex impairs metacognitive visual awareness. Cogn Neurosci 1:165–175.

Sandberg K, Timmermans B, Overgaard M, Cleeremans A (2010): Measuring consciousness: Is one measure better than the other? Conscious Cogn 19:1069–1078.

Sandberg K, Bahrami B, Kanai R, Barnes GR, Overgaard M, Rees G (2013): Early visual responses predict conscious face perception within and between subjects during binocular rivalry. J Cogn Neurosci 25:969–985.

Schmitt GJ, Frodl T, Dresel S, la Fougere C, Bottlender R, Koutsouleris N, Hahn K, Moller HJ, Meisenzahl EM (2006): Striatal dopamine transporter availability is associated with the productive psychotic state in first episode, drug-naive schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 256:115–121.

Schwarz G (1978): Estimating the dimension of a model. Ann Stat 6:461–464.

Seth AK (2010): A MATLAB toolbox for Granger causal connectivity analysis. J Neurosci Methods 186:262–273.

Spedicato GA (2014): Markovchain: An R package to easily handle discrete Markov chains. R package version 0.0.9.5, http://cran.r-project.org/web/packages/markovchain/

Tang YY, Lu Q, Geng X, Stein EA, Yang Y, Posner MI (2010): Short-term meditation induces white matter changes in the anterior cingulate. Proc Natl Acad Sci USA 107:15649–15652.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289.

Ward RD, Simpson EH, Richards VL, Deo G, Taylor K, Glendinning JI, Kandel ER, Balsam PD (2012): Dissociation of hedonic reaction to reward and incentive motivation in an animal model of the negative symptoms of schizophrenia. Neuropsychopharmacology 37:1699–707.

Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H (2011): Amping up effort: Effects of d-amphetamine on human effort-based decision-making. J Neurosci 31:16597–1602.

Watson AB, Pelli DG (1983): QUEST: A Bayesian adaptive psychometric method. Perception Psychophys 33:113–120.

Wise RA, Bozarth MA (1985): Brain mechanisms of drug reward and euphoria. Psychiatr Med 3:445–460.